

# **EXHIBIT 144**



ANNUAL PRODUCT REVIEW  
Digoxin Tablets, USP 0.125 mg

**ANNUAL PRODUCT REVIEW**  
**FOR**  
**Digoxin Tablets, USP 0.125mg**  
**01/01/08-12/31/08**  
**Product Code: 145**

Written By:  
Urszula Mioduszewski  
Specialist, Quality Assurance

Signature

Date

Reviewed By:  
Michael Redmond  
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Signature

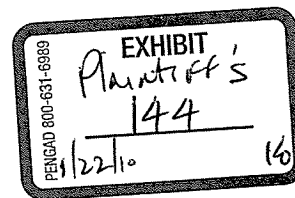
Date

Approved By:

Director, Quality Assurance

Signature

Date



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## 1 SUMMARY

The manufacture of nineteen batches of Digoxin Tablets, USP 0.125 mg was completed during the period from 01/01/08 to 12/31/08; eight batches were rejected (see Section 3 below); all other lots were found acceptable for commercial distribution.

There were three Critical Deviations, three Major Deviations, three Planned Deviations, and no Laboratory OOS Investigations for the referenced product during the subject review period. See Section 9.

There were twenty two Adverse Events/Product Complaints and twenty seven Product Complaints received for the referenced product during the subject review period. See Section 11.

There were two Change Controls issued for the referenced product during the subject review period. See Section 13.

There were no Field Alerts issued during the subject review period. All in-date lots of the referenced product have been recalled. See Section 15.

Stability data support the current expiry dating of the product. See Section 16.

There was a Validation Study performed for the referenced product during the subject review period. See Section 17.

This product has been indefinitely discontinued as a result of the 2008 FDA inspection. This is the last APR for this product until manufacturing activity resumes.

## 2 TIME PERIOD COVERED

All batches of the referenced product with a Completion Date from 01/01/08 to 12/31/08 are included in this Annual Product Review.

## 3 NUMBER OF BATCHES MANUFACTURED

Nineteen batches of the referenced product were manufactured during the subject review period. Details are in Table 1.

Table 1: Batches Manufactured

Batch Number	MF Version #	Completion Date	Final Disposition	
			Status	Date
80044A	14504(08)	23-Jan-08	Released	4-Mar-08
80045A	14504(08)	25-Jan-08	Released	4-Feb-08
80046A	14504(08)	28-Jan-08	Released	6-Feb-08
80047A	14504(08)	31-Jan-08	Released	4-Feb-08
80050A <sup>1</sup>	RV14501(00)	31-Jan-08	Rejected	28-May-08
80051A <sup>2</sup>	RV14501(00)	10-Feb-08	Rejected	16-Jun-08
80052A <sup>1</sup>	RV14501(00)	20-Feb-08	Rejected	28-May-08
80053A <sup>2</sup>	RV14501(00)	15-Feb-08	Rejected	16-Jun-08
80137A <sup>1</sup>	RV14501(00)	25-Feb-08	Rejected	28-May-08
80138A <sup>1</sup>	RV14501(00)	29-Feb-08	Rejected	28-May-08
80189A	14504(08)	8-Mar-08	Released	15-Mar-08



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80190A	14504(08)	12-Mar-08	Released	19-Mar-08
80191A	14504(08)	14-Mar-08	Released	24-Mar-08
80192A	14504(08)	18-Mar-08	Released	26-Mar-08
80202A	14504(08)	19-Mar-08	Released	28-Mar-08
80224A	14504(08)	21-Mar-08	Released	31-Mar-08
80226A <sup>3</sup>	14504(08)	N/A	Rejected	22-May-08
80227A	14504(08)	25-Mar-08	Released	31-Mar-08
80228A <sup>4</sup>	14504(08)	27-Mar-08	Rejected	24-Jul-08

- Note(s):**
- 1 Batch #s 80050A, 80137A, 80138A and 80052 were rejected as a part of the 2008 site-wide recall; refer to Rejection #R08-028.
  - 2 Batch #s 80051A and 80053A were rejected as a part of the 2008 site-wide recall; refer to Rejection # R08-031.
  - 3 Batch # 80226A was rejected as a part of the 2008 site-wide recall; refer to Rejection # R08-027.
  - 4 Batch # 80228A was rejected because of the OOS weight on filled bottles; refer Rejection # R08-058.

#### 4 PRODUCT DESCRIPTION

Yellow, round bisected tablets, debossed "A 145" or "B 145" on the bisected side.

#### 5 IN-PROCESS RESULTS

##### 5.1 Blending

Table 2: Blend Results

Variable	Specification	2008 Result	2007 APR Result	2006 APR Result	C <sub>pk</sub>
Blend Yield	95.0-101.0%	99.9% 99.8-100.0% 0.06	N/A	N/A	5.9
Blend Reconciled	N/A	99.9% 99.8-100.0% 0.06	N/A	N/A	N/A

**Note(s):** 1 N/A



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Figure 1 Blend Yield by Batch

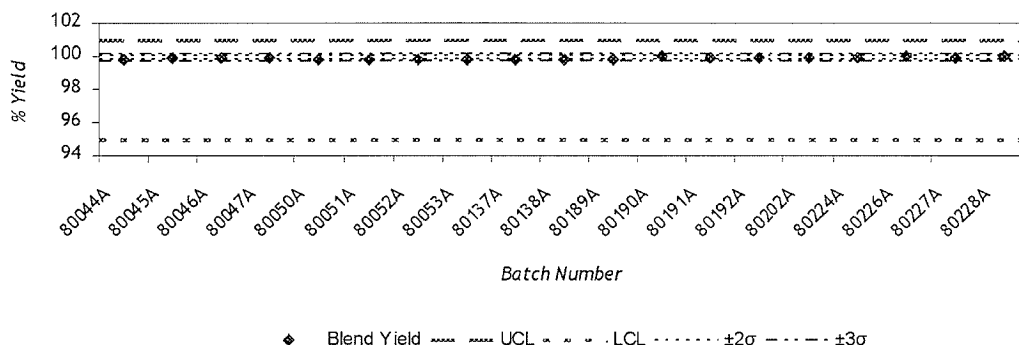
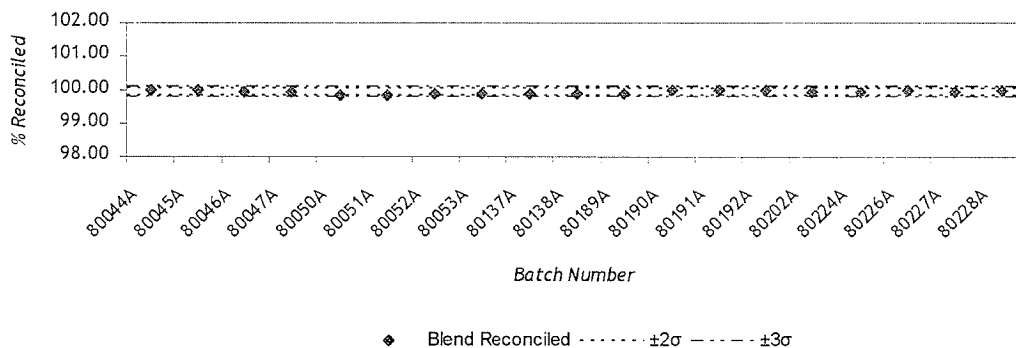


Figure 2 Blend Reconciled by Batch



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## 5.2 Compression

Table 3: Compression Results

Variable	Specification	2008 Result	2007 APR Result	2006 APR Result	C <sub>pk</sub>
Weight, Individual	0.097-0.113 g	0.106g 0.100-0.111 g 0.0	0.106 g 0.101-0.112 g 0.0	0.106 g 0.100-0.111 g 0.0	0.7
Tablet Weight RSD	N/A	1.3% 1.0-1.5% 0.1	N/A	N/A	N/A
Hardness	1.0-6.0 kp	4.3 kp 3.0-5.7 kp 0.2	4.2 kp 2.5-6.3kp <sup>1</sup> 0.2	4.3 kp 2.8-6.0kp 0.1	3.4
Thickness	2.00-3.00mm	2.71 mm 2.55-2.90 mm 0.02	2.71 mm 2.20-2.89 mm 0.02	2.7 mm 2.00-2.85 mm 0.02	4.1
Finished Product Yield	95.0-101.0%	99.1% 98.0-99.5% 0.5	99.2% 97.8-99.5% 0.4	99.5 % 98.9-99.8 % 0.2	1.3
Finished Product Reconciled	97.0-101.0%	99.8% 99.5-100.2% 0.2	N/A	N/A	2.7

Note(s): 1 In the 2007 APR batch # 70078A was reported with a high hardness of 6.3 kp.

Figure 3 Tablet Weight by Batch

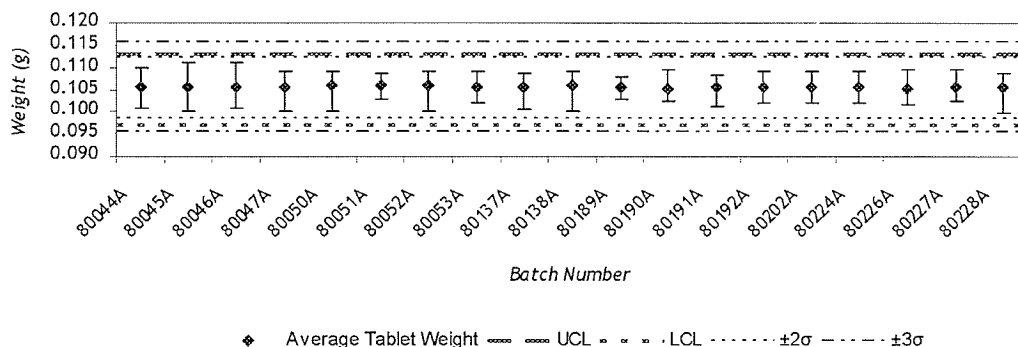




Figure 4 Tablet Weight RSD by Batch

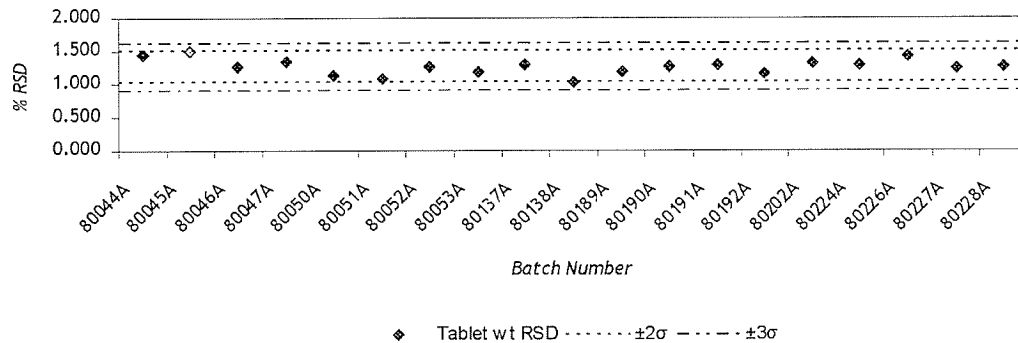


Figure 5 Tablet Hardness by Batch

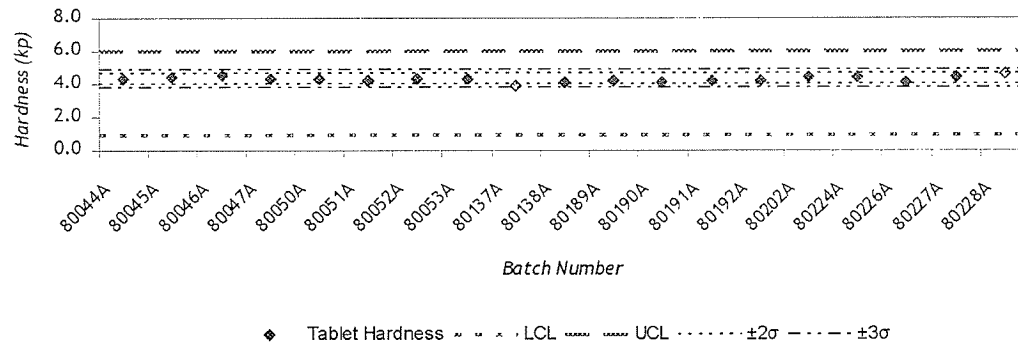


Figure 6 Tablet Thickness by Batch

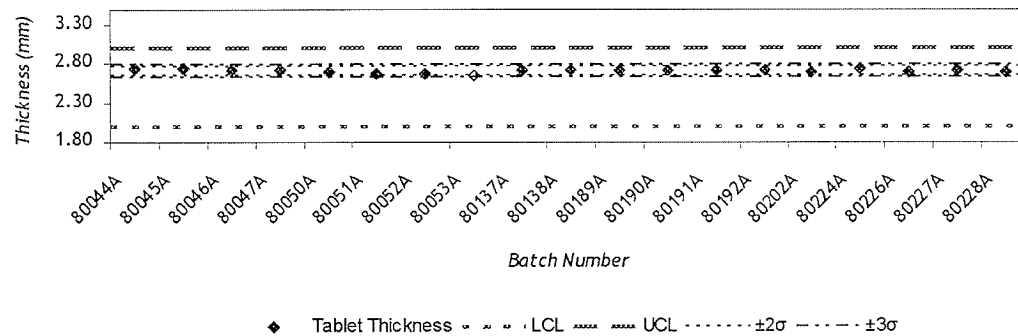




Figure 7 Finished Product Yield by Batch

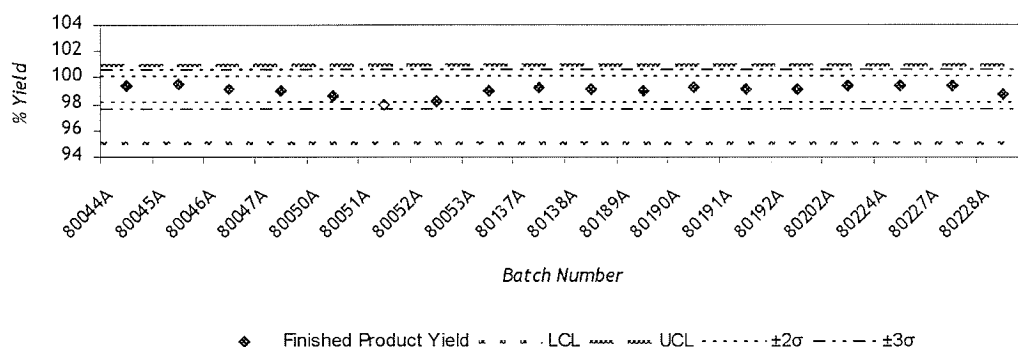
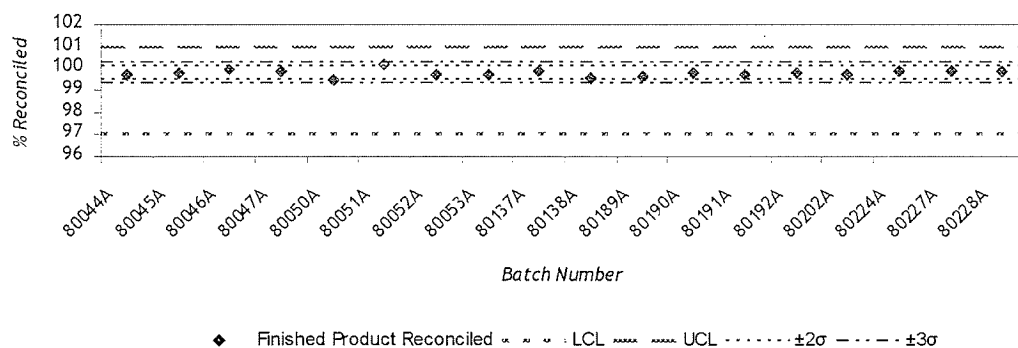


Figure 8 Finished Product Reconciled by Batch



## 6 QC ANALYTICAL TESTING RESULTS

### 6.1 Blend Testing

Table 4: Blend Testing Results

Variable	Specification	2008 Result	2007 APR Result	2006 APR Result	C <sub>pk</sub>
Average Blend Assay	90.0-110.0%	99.0% 94.1-103.1% 2.5	98.6% 92.3-104.1% 2.4	97.7% 95.9-100.3% 1.0	1.2
Blend Assay RSD	NMT 5.0%	1.4% 0.7-2.3% 0.6	1.5% 0.4-4.0% 0.7	1.7% 0.6-3.8% 0.7	2.2

Note(s): N/A



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Figure 9 Average Blend Uniformity by Batch

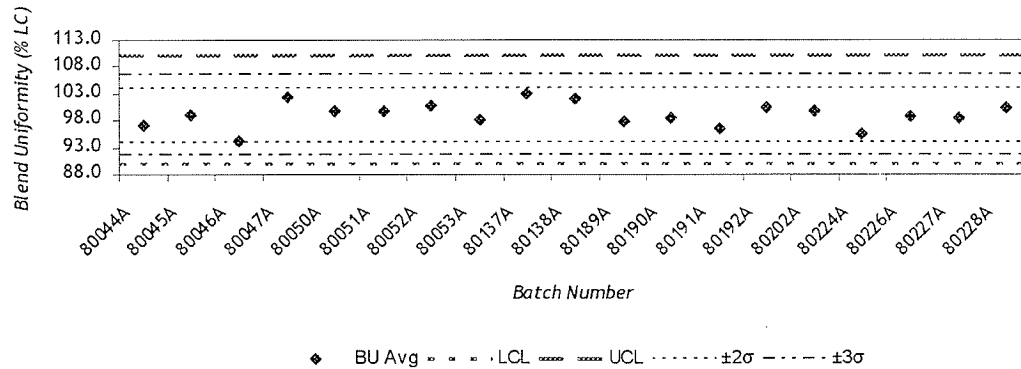
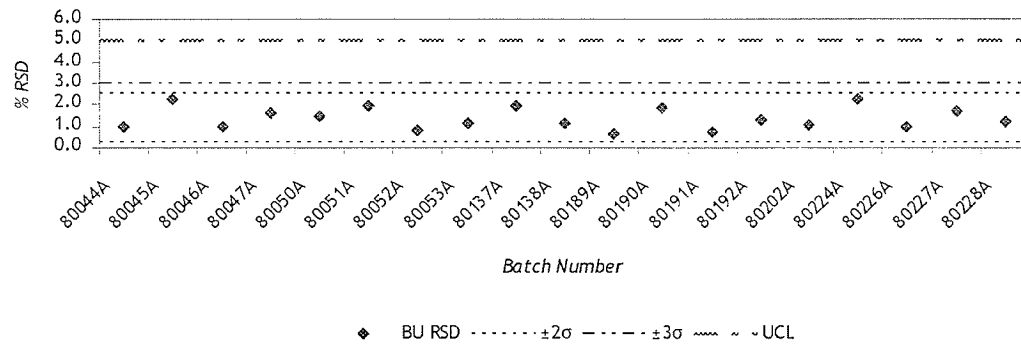


Figure 10 Blend Uniformity RSD by Batch



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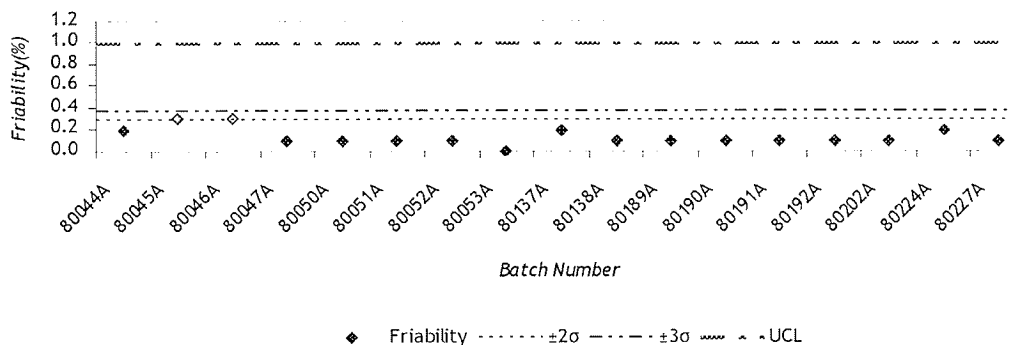
## 6.2 Finished Product Testing

Table 5: Finished Product Testing Results

Variable	Specification	2008 Result	2007 APR Result	2006 APR Result	C <sub>pk</sub>
Friability	NMT 1.0%	0.1% 0.0-0.3% 0.1	0.1% 0.0-0.3% 0.06	0.1% 0.1-0.2% 0.03	3.8
Average Assay	90.0-105.0%	98.8% 95.7-102.2% 2.0	98.0% 94.5-101.9% 1.9	99.3% 96.6-101.7% 0.9	1.5
Average Content Uniformity	N/A	99.5% 94.7-103.3% 2.1	99.6% 96.1-104.3% 1.9	99.1% 95.8-102.2% 1.5	N/A
Content Uniformity Acceptance Value	NMT 15.0%	4.3% 1.1-9.2% 1.9	4.8% 2.4-11.3% 1.8	1.9% RSD <sup>1</sup> 1.0-3.1% RSD <sup>1</sup> 0.4	1.9
Dissolution Average	NLT-80% (Q) in 60 minutes	98.8% 93.7-101.2% 2.1	98.8% 95.8-102.3% 1.6	99.6% 97.6-101.3% 0.8	2.9
Digoxigenin	NMT 2.0%	0.2% 0.1-0.5%	N/A	N/A	N/A
Digoxigenin Bisdigitoxoside	NMT 2.0%	0.3% 0.2-0.4%	N/A	N/A	N/A

Note(s): 1 Prior to the 2007 APR, RSD was reported instead of Acceptance Value; RSD values from the 2006 are presented.

Figure 11 Friability by Batch



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Figure 12 Average Assay by Batch

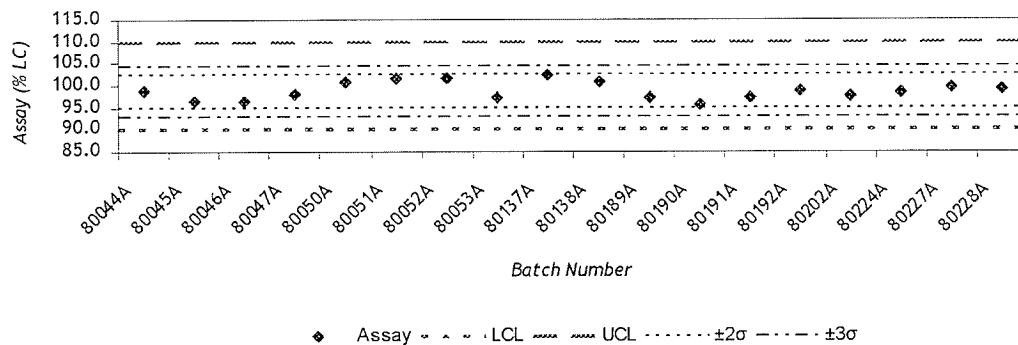


Figure 13 Average Content Uniformity by Batch

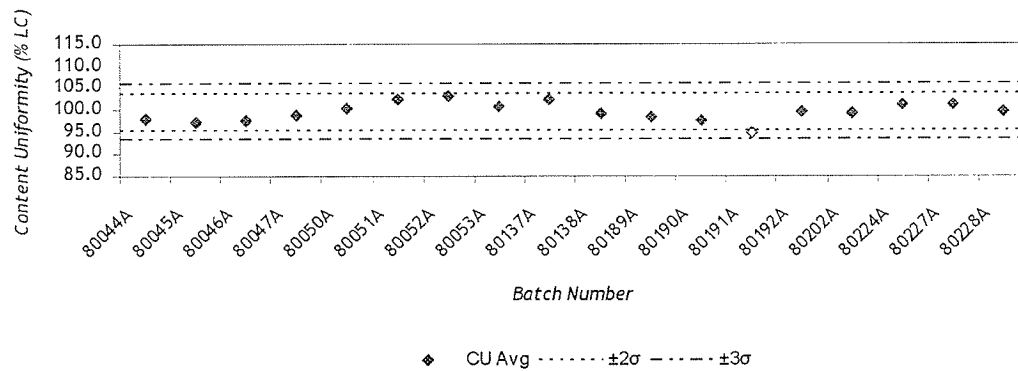
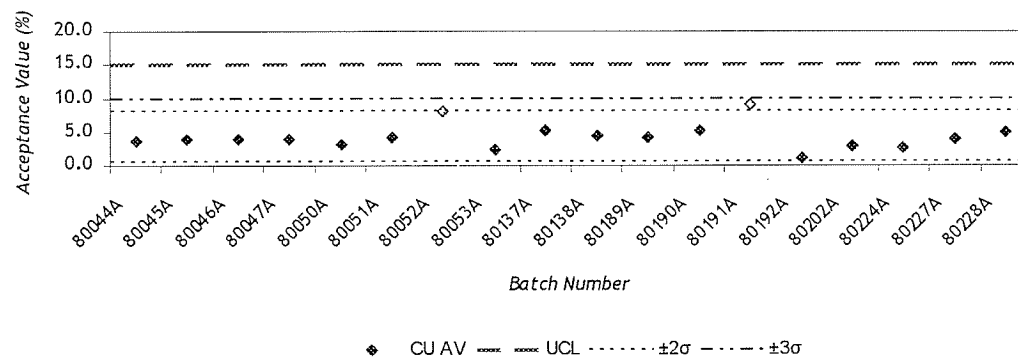


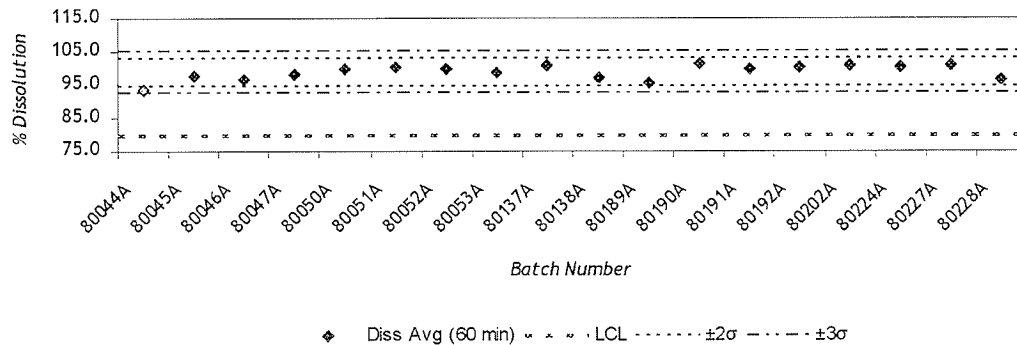
Figure 14 Content Uniformity Acceptance Value by Batch





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Figure 15 60-Minute Dissolution Average by Batch



## 7 PRODUCT ACTIVE PHARMACEUTICAL INGREDIENT (API) REVIEW

The referenced product uses one API Digoxin Micronized, USP.

No OOS results were observed for the API during the subject review period.

## 8 STATISTICAL ANALYSIS/INTERPRETATION

For products with more than 20 batches to analyze, a trend is  $C_{pk}$  less than 1.0 and more than one similar observation outside of  $\pm 3$  standard deviations of the mean, two or more similar observations outside of  $\pm 2$  standard deviations of the mean in five consecutive batches, four or more similar observations outside of  $\pm 2$  standard deviations of the mean in 10 consecutive batches, or more than five similar observations outside of  $\pm 2$  standard deviations of the mean in the subject review period.

Statistical analysis of process parameters, and in-process and finished product analytical testing results indicates no trends for the referenced product during the subject review period.

Control plots of analysed data, including specification limits, may be found in Section 5 and 6, above.

## 9 DEVIATION REVIEW

Deviations are departures from regulations, standards, policies, procedures, batch records, methods, specifications, written requirements, etc. or any observation that has the potential to impact the SQIPS of a product.

A detailed listing of Deviation Reports is attached.

### 9.1 Critical Deviations

A Critical Deviation is any deviation of a product already in distribution.

There were three Critical Deviations for the referenced product during the subject review period. See the attached report for details.

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Batch #s 70023A1/AQ, 70078A1, 70081A2, 71049AQ/AQ1, 71050A1/AQ, 71051A1/AQ were exposed to a low humidity excursion during stability. See investigation # 08-055.

Batch #s 70023A1/AQ, 70078A1, 70081A2, 71049AQ/AQ1, 71050A1/AQ, 71051A1/AQ were exposed to OOS temperature during stability. See investigation # 08-197.

Batch #s 70023A1/AQ, 70078A1, 70081A2, 71049AQ/AQ1, 71050A1/AQ, 71051A1/AQ were exposed to out of range humidity and temperature during stability. See investigation # 08-206.

## 9.2 Major Deviations

A major deviation is any deviation that impacts the SQIPS of a product not yet in distribution, that had the potential to impact SQIPS but (through investigation) was justified to have no impact, or that is associated with an out-of-specification result with no root cause.

There were three Major Deviations for the referenced product during the subject review period. See the attached report for details.

Batch # 80051A, machine operator observed oil spots for drums # 5 and # 6 during compression. See investigation # 08-017.

For batch # 80053A compression operator did not record the metal detector test for the end of the run on 02/15/08. See investigation # 08-028.

For batch # 80228A1 filled bottles in packaging exceeded weight specification limits. See investigation # 08-060.

## 9.3 Planned Deviations

A planned deviation is any planned departure from the routine manufacturing, testing, or release requirements for a product.

There were three Planned Deviations for the referenced product during the subject review period; one to allow the current food grade compression machine lubricant to be replaced with a slightly more viscous food grade lubricant from the same oil manufacturer; one allow to add static eliminator to air purge nozzle on BOSS- Pack counter machine on line 403 to prevent powder from sticking to the counter head; and one to allow in-process friability testing to be performed by manufacturing instead of the QC Lab. See the attached report for details.

## 9.4 Laboratory Out of Specification (OOS) Investigations

There were no laboratory OOS investigations issued for the referenced product during the subject review period.

# 10 OUT-OF-SPECIFICATION REVIEW

There were no out-of-specification results for the referenced product during the subject review period.

# 11 COMPLAINTS

There were twenty two Adverse Event/Product Complaints and twenty seven Product Complaints received for the referenced product during the subject review period. See the attached report for details.

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## **12 BATCH REJECTIONS**

There were eight batches of the referenced product rejected during the subject review period. See section 3 above.

## **13 CHANGE CONTROL REVIEW**

There were two approved Change Controls issued for the referenced product during the subject review period. See the attached report for details.

## **14 RETURNED GOODS**

Actavis Totowa, LLC contract manufactures the referenced product for Mylan Pharmaceuticals: Mylan Pharmaceuticals manages their own product returns. There were no returns reported to Actavis Totowa, LLC for the referenced product during the subject review period.

## **15 RECALLS/FIELD ALERTS**

The referenced product was the subject of a recall during the subject review period. Refer to the attached report for details.

No Field Alerts were issued for the referenced product during the subject review period.

## **16 STABILITY**

Eight batches of the referenced product were evaluated for Room Temperature stability evaluation in 100-count bottles; six of those batches were also evaluated in 5000-count bottles during the subject review period. Detailed results of the stability program are attached. All batches of the referenced product have been removed from stability per change control C0283. Stability data support the current expiry dating of the product.

## **17 VALIDATION**

A Validation Statement is attached and indicates that Process Validation was performed for the referenced product during the subject review period. See the attached report for details.

## **18 UNRESOLVED ISSUES FROM PREVIOUS ANNUAL PRODUCT REVIEWS**

There are no unresolved action items from previous Annual Product Reviews.

## **19 CONCLUSIONS AND RECOMMENDATIONS**

As a result of the 2008 FDA Inspection, this product is the subject of a voluntary recall and has been indefinitely discontinued. This is the last Annual Product Review for this product.



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## Cover Sheet for Summary Attachments

The following are a list of Annual Status Reports for Digoxin Tablets, USP 0.125 mg which are included as attachments to this Annual Product Review Report.

**Required and attached**

**Attachment by:**

API Complaints Report	<input type="checkbox"/>	_____
Deviation Investigations Report	<input type="checkbox"/>	_____
Laboratory OOS Investigations Report	<input type="checkbox"/>	_____
Planned Deviations Report	<input type="checkbox"/>	_____
Customer Complaints Report	<input type="checkbox"/>	_____
Change Control Status Report	<input type="checkbox"/>	_____
Product Return and Salvage Report	<input type="checkbox"/>	_____
Recalls Report	<input type="checkbox"/>	_____
Field Alerts Report	<input type="checkbox"/>	_____
Stability Report	<input type="checkbox"/>	_____
Process Evaluation, Cleaning & Process Validation Report	<input type="checkbox"/>	_____
Summary Data Tables	<input type="checkbox"/>	_____

Annual Status Reports

Reviewed & Approved by: \_\_\_\_\_ Date: \_\_\_\_\_

Quality Engineer, Quality Assurance

Approved by: \_\_\_\_\_ Date: \_\_\_\_\_

Director, Quality Assurance

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